Complete Summary

GUIDELINE TITLE

2006 national guideline for the management of lymphogranuloma venereum.

BIBLIOGRAPHIC SOURCE(S)

Clinical Effectiveness Group, British Association for Sexual Health and HIV (BASHH). National guideline for the management of lymphogranuloma venereum (LVG). London (UK): British Association for Sexual Health and HIV (BASHH); 2006. 14 p. [40 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previously released version: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guideline for the management of lymphogranuloma venereum. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. [28 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Lymphogranuloma venereum, a *Chlamydia trachomatis* infection (also known as Durand-Nicolas-Favre's disease, lymphopatia venereum, and lymphogranuloma inguinale)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Infectious Diseases
Obstetrics and Gynecology
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To assist practitioners in managing men and women diagnosed with lymphogranuloma venereum (LGV)

TARGET POPULATION

Patients in the United Kingdom with lymphogranuloma venereum (LGV)

INTERVENTIONS AND PRACTICES CONSIDERED

Assessment/Diagnosis

1. Assessment of clinical features
2. Collection of genital specimens containing cellular material
3. Laboratory diagnostic techniques:
    - Deoxyribonucleic acid (DNA) amplification techniques (NAATs) such as the ligase chain reaction (LCR) or polymerase chain reaction (PCR)
    - Culture on cycloheximide treated McCoy cells
    - Chlamydia trachomatis serology. Complement fixation test, the single L-type immunofluorescence test, and the micro-immunofluorescence test
    - Other diagnostic techniques considered, but not specifically recommended include direct immunofluorescence (DIF), enzyme immunoassay (EIA), and histology
    - Genotyping to distinguish LGV strains
4. Screening for other genital ulcerative diseases, e.g., *Haemophilus ducreyi, Treponema pallidum, Herpes simplex* and *Klebsiella/Calymmatobacterium granulomatis*
5. Screening for human immunodeficiency virus (HIV) and hepatitis C infection and other sexually transmitted infections
6. Lymph node biopsy for differential diagnosis

Treatment/Management

1. Counseling and patient education

2. Pharmacological interventions:
    - Doxycycline
    - Erythromycin
    - Co-trimoxazole
    - Tetracycline
    - Minocycline
    - Azithromycin (clinical data on its use is lacking)
3. Fluctuant buboes aspirated through healthy adjacent skin
4. Clinical follow-up until signs and symptoms have resolved
5. Laboratory follow-up (microbiological tests of cure, NAAT)
6. Surgical repair, including reconstructive genital surgery
7. Sexual partner examination, testing for rectal, urethral or cervical chlamydial infection, and treatment as needed

MAJOR OUTCOMES CONSIDERED

- Labour intensiveness, expense, sensitivity, specificity, and availability of diagnostic techniques
- Efficacy and cost of pharmacological treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The previous guidelines (1998, 2000) were largely based on the published U.S. Centers for Disease Control and Prevention (CDC) Guidelines for Treatment of Sexually Transmitted Diseases of 1993 and 1997, and on a Medline search spanning the years 1966-2000. The guideline has been updated by searching Medline from 2000-2005 using the search terms: "Lymphogranuloma venereum"; "*Chlamydia trachomatis* diagnosis"; and "*Chlamydia trachomatis* treatment." The most recent CDC guidelines (2002) were also consulted. There were no entries in the Cochrane Library of any randomized clinical trials on lymphogranuloma venereum. In addition abstracts and proceedings from the International Conferences on AIDS, Symposia on Human Chlamydial Infections, Meetings of the International Society for STD Research (ISSTDR), including the most recent meeting held in Amsterdam (July 2005), or the British Association for Sexual Health and HIV (BASHH) Spring Meeting held in Nottingham, May 2006, were reviewed.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Ia: Evidence obtained from meta-analysis of randomised controlled trials
Ib: Evidence obtained from at least one randomised controlled trial
IIa: Evidence obtained from at least one well designed controlled study without randomisation
IIb: Evidence obtained from at least one other type of well designed quasi-experimental study
III: Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies
IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading of Recommendations

A (Evidence Levels Ia, Ib)

- Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence Levels IIa, IIb, III)

- Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

C (Evidence Level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities.
- Indicates absence of directly applicable studies of good quality.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Microbiologists, clinicians, and epidemiologists at the Health Protection Agency in Colindale, London, the Regional Microbiology Laboratory, Plymouth, Devon, the HIV/STI Centre at University College London Medical School (UCLMS), and the London School of Hygiene & Tropical Medicine (LSHTM) have been consulted.

The guidelines were posted for three months for general consultation on the British Association for Sexual Health and HIV (BASHH) website (www.bashh.org) before finalization by the Clinical Effectiveness Group (CEG).

The rare nature of this disease precluded patient's consultation.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Levels of evidence (I-IV) and grades of recommendation (A-C) are defined at the end of the "Major Recommendations" field.

New Information in This Guideline Since 2003 Publication

Aetiology and Epidemiology

- Latest data from lymphogranuloma venereum (LGV) outbreaks in Western Europe (including United Kingdom [UK]) and United States.
- Epidemics have affected gay clubs sex scene, with no indication of contacts with endemic countries for LGV.
- Cases were White men who have sex with men (MSM), many of whom were also known to be human immunodeficiency virus (HIV) positive and co-infected with hepatitis C virus (HCV).

Diagnosis

- Successful use of molecular diagnostic techniques to detect *Chlamydia trachomatis* serovars: use of nested polymerase chain reaction (PCR) for the

detection of the major *omp-1* gene of *C trachomatis*, and restriction fragment length polymorphism (RFLP) analysis to perform serovar typing on anorectal swabs.
- Clinical features have been diagnostic in recent outbreak in MSM with severe proctocolitis and rectal bleeding with history of genital ulcer and/or lymphadenopathy.

Management

- UK cases have been successfully treated with doxycycline 100 mg twice a day (BD) for 3 weeks.
- Dutch cases have been successfully treated with a single dose azithromycin 1.0 g.
- Enhanced surveillance put in place by the UK's Health Protection Agency (HPA).

Diagnosis

The diagnosis of LGV is often differential, after other causes of genital ulceration or inguinal lymphadenopathy have been ruled out. In the case of ano-rectal syndrome, diagnosis is based on clinical suspicion (e.g., combination of signs of proctocolitis, inguinal lymphadenopathy, and history of genital ulcer would be highly evocative) after the exclusion of other aetiologies of rectal bleeding. Even when LGV is suspected, investigations for other potentially co-existing sexually transmitted infections must be undertaken, in particular for syphilis.

Positive diagnosis of LGV is difficult, requiring a combination of good clinical acumen and supportive investigations. LGV can be suspected on positive chlamydia serology, isolation of *Chlamydia trachomatis* either from the infected site or histological identification of Chlamydia in infected tissue. Traditional methods for LGV diagnosis have been reviewed elsewhere, but the modern techniques are now based on nucleic acid amplification tests (NAATs).

Collection of Genital Specimens

Chlamydiae are intracellular organisms so samples must contain cellular material that can be obtained:

- From the ulcer base exudate or from rectal tissue
- By aspiration from fluctuant lymph nodes/buboes; after topical disinfection, a 20 gauge needle should be inserted into the lymph node through healthy adjacent tissue and the pus aspirated into a syringe; saline solution may be injected and re-aspirated; bubo pus is best homogenised in tissue culture medium before inoculation.
- Rectal swabs from MSM and women exposed rectally should be collected as recommended in the Health Protection Agency (HPA) guidelines.
- A urethral swab or first-catch urine sample can be used when lymphadenopathy is present and LGV is suspected as the cause.

Main Diagnostic Techniques

i. *Detection of nucleic acid (DNA)* by amplification techniques (NAATs) such as the ligase chain reaction (LCR) or the polymerase chain reaction (PCR); these methods are becoming established for routine testing of urethral, cervical, or urine specimens but have rarely been used in the context of LGV, until the recent outbreaks in Western Europe; they are highly sensitive and specific, and have now widely become available commercially. Positive samples should be confirmed by real-time PCR for LGV specific DNA.

or

ii. *Culture* on cycloheximide treated McCoy cells of material from LGV lesion is the most specific method, but its sensitivity is 75-85% at best, and often closer to 30-50% in the case of bubo aspirate; this is in part due to the toxic effect of the pus on the culture cells; the method is labour intensive, expensive, and of restricted availability.

or

iii. *Chlamydia trachomatis serology*. Three types of techniques have been used: complement fixation (CF) test, the single L-type immunofluorescence test, and the micro-immunofluorescence test (micro-IF), the latter one being the most accurate serological assay. In general, a four-fold rise of antibody (both immunoglobulin M [IgM] and immunoglobulin G [IgG]) in the course of suspected illness is diagnostic of active infection. Alternatively, single point titres of $\geq$1/64 and $\geq$1/256 have been considered positive, as only an invasive infection such as that caused by LGV could be responsible for such high titres. The test may lack sensitivity for the earlier manifestations of LGV such as ulcers, and a high titre in the absence of symptoms cannot confirm LGV. It is only performed in a few specialised laboratories.

Other Methods

- The original diagnostic method for LGV from the 1930s until 1970s was the *Frei test*, which consisted of intradermal injections of purified *Chlamydia trachomatis* antigen obtained from culture in yolk sacs of chicken embryos. The test was reportedly positive in about 95% of bubonic LGV or late complications. Given its lack of sensitivity and specificity, the commercial manufacture of the test has been abandoned in 1974.
- *Direct immunofluorescence (DIF)* of material from a suspected LGV lesion to demonstrate *Chlamydia trachomatis* elementary and inclusion bodies; this method can be sensitive but requires expertise (subjective interpretation) and is labour intensive.
- *Enzyme immunoassay (EIA)* sensitivity is lower than other methods and it is no longer recommended.
- Histology of the lymph nodes shows follicular hyperplasia and abscesses and is not specific.
- In a recent study of 12 anorectal biopsies from MSM with LGV, cryptitis and crypt abscesses, without distortion of crypt architecture, were the most common findings.

Typing to distinguish LGV strains from other chlamydial serotypes is becoming available. Investigators in Sheffield and Durban were able to combine several

molecular diagnostic techniques, using PCR detecting the major outer membrane protein (*momp-1*) gene of *Chlamydia trachomatis* and restriction fragment length polymorphism (RFLP) analysis to perform serovar typing from the patient's lymph node aspirates, or ulcers. Sequencing, which is increasingly widely available commercially, is the method now recommended by the HPA for genotyping. These techniques have been applied with great success on anorectal swabs collected from patients with proctitis during the recent LGV outbreaks in Western Europe. All these patients have been confirmed to have L2 serovar.

Management

General Advice

1. Patients should be advised to avoid unprotected sexual intercourse until they and their partner(s) have completed treatment and follow-up.
2. Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information.

Further Investigations

Screening for other possible causes of genital ulcerative disease should be arranged, i.e., diagnosis of *Haemophilus ducreyi, Treponema pallidum, Herpes simplex* and *Klebsiella/Calymmatobacterium granulomatis*. Many cases of the recent LGV outbreaks in Europe were associated with human immunodeficiency virus (HIV) and hepatitis C infection and other sexually transmitted infections (STIs) (e.g., gonorrhoea), and screening for these infections (and possibly also for syphilis) is therefore strongly encouraged, after appropriate counseling.

Lymph node biopsy may be used to make differential diagnoses with atypical infections and neoplasia.

Treatment

Early treatment is important to reduce the chronic phase. Prolonged treatment (at least 3 weeks) is the norm and more than one course of therapy (see table below), alternating antibiotics may be necessary for chronic cases.

On the basis of the known response of *Chlamydia trachomatis* to antibiotics such as doxycycline, tetracycline, erythromycin in uncomplicated infections, the following recommendations have been made (see table below for summary of these recommendations):

Recommended Regimens

- 1st choice: doxycycline 100 mg twice daily orally for 21 days (or tetracycline 2 g daily or minocycline 300 mg loading dose followed by 200 mg twice daily) (**III or IV**, **B**)
- 2nd choice: erythromycin 500 mg four times daily orally for 21 days (**IV**, **B**)

Alternative Regimens

The activity of azithromycin against *Chlamydia trachomatis* suggests that it may be effective in multiple doses over 2-3 weeks but clinical data on its use are lacking.

Cases during the recent LGV outbreaks were successfully treated with standard 3-week courses of doxycycline and in some instances with azithromycin 1.0 g as a single dose (**IV**, **C**). Clearly, the current outbreaks afford the opportunity to conduct randomized comparative trials of newer/shorter drug regimens.

Special mention should be made of the treatment of non-LGV *Chlamydia* strains found on rectal samples, sometimes among asymptomatic patients. There are currently no specific guidelines for the management of such patients. Discussions held at the recent British Association for Sexual Health and HIV (BASHH) meeting among genitourinary medicine (GUM) physicians in the United Kingdom (BASHH Spring Meeting, Nottingham, 17-19 May 2006) suggested that prolonged treatment with doxycycline could be provided.

Allergy

Patients allergic to tetracyclines should be treated with the erythromycin regimen.

Treatment for Pregnant or Lactating Mothers

Pregnant and lactating women should be treated with the erythromycin regimen.

Accompanying Measures

Fluctuant buboes should be aspirated through healthy adjacent skin and surgical incision is usually contraindicated by fear of complications.

Sexual Partner(s) Management

Persons who have had sexual contacts with a patient who has LGV within the 30 days* before onset of the patient's symptoms should be examined, tested for rectal, urethral, or cervical chlamydial infection (as applicable), and treated, or receive presumptive treatment (e.g., azithromycin 1.0 g orally or doxycycline 100 mg twice daily for 7 days have been used).

*Note: An extended period up to 6 months was proposed in the European outbreaks investigations, resulting in little success in terms of increased number of partners traced.

Follow-up

Patients should be followed clinically until signs and symptoms have resolved. This may occur within 3-6 weeks. However, there is also evidence of spontaneous remission within 8 weeks. Routine microbiological test of cure will depend on locally available resources. Specific NAAT tests can be used, although their use

has not yet been rigorously evaluated. The optimum time for testing is not yet known.

Patients with fibrotic lesions or fistulas are beyond the stage where chemotherapy can be used and surgical repair, including reconstructive genital surgery, often must be considered.

Special Considerations

Latent LGV may be reactivated in patients with HIV infection with development of multiple abscesses. HIV infected patients should be treated following the regimens previously cited. It had been suggested that prolonged therapy may be required and delay in resolution may occur. However, data from the recent LGV epidemics in Europe and data from South Africa showed that HIV-1 co-infection was not associated with a decreased response to treatment.

Table. Drugs Shown to be Effective in the Treatment of Lymphogranuloma Venereum (modified by the National Guideline Clearinghouse [NGC])

Drug	Dose	Route	Grading of Recommendation	Level of Evidence
Co-trimoxazole (trimethoprim/sulfamethoxazole)	80 mg/400 mg twice daily x 21 days	Oral	**C**	**IV**
Doxycycline*	100 mg twice daily x 21 days	Oral	**B/C**	**IV**
Erythromycin*	500 mg four times daily x 21 days	Oral	**C**	**IV**
Minocycline	300 mg loading dose, followed by 200 mg twice daily x 21 days	Oral	**C**	**IV**
Tetracycline hydrochloride	500 mg four times daily x 21 days	Oral	**C/B**	**III**
Azithromycin	1.0 g STAT	Oral	**C**	**IV**
	1.0 g daily x 21 days	Oral	**C**	**IV**

Note: There have been numerous randomised trials to prove the equivalent efficacies of doxycycline, erythromycin, tetracycline, minocycline, etc, for the management of uncomplicated *Chlamydia trachomatis* infections. However these are lacking for LGV; a B grade is conferred for simplicity of use for doxycycline.

*Recommended by U.S. Centers for Disease Control and Prevention

Definitions:

Levels of Evidence

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A (Evidence Levels Ia, Ib)

- Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence Levels IIa, IIb, III)

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C (Evidence Level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities.
- Indicates absence of directly applicable studies of good quality.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

No controlled double blind treatment trials have been published on lymphogranuloma venereum. The type of supporting evidence is graded and identified for select recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate diagnosis and management of patients with lymphogranuloma venereum
- Early treatment is important to reduce the chronic phase of the condition

POTENTIAL HARMS

Allergic reaction to tetracyclines

CONTRAINDICATIONS

CONTRAINDICATIONS

Surgical incision of fluctuant buboes is usually contraindicated by fear of complications.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- No controlled double blind treatment trials have been published on lymphogranuloma venereum. The low incidence of the disease, its complex presentation, and its natural history, marked by spontaneous remissions and exacerbations, have precluded any rigorous evaluation of management.
- Suggestions for diagnostic approach made in this guideline should be tailored to local resources. DNA amplification tests and the serological tests recommended may not be available in all laboratories. Additional testing may be available from the Sexually Transmitted Bacteria Reference Laboratory.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Chart Documentation/Checklists/Forms
Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Clinical Effectiveness Group, British Association for Sexual Health and HIV (BASHH). National guideline for the management of lymphogranuloma venereum (LVG). London (UK): British Association for Sexual Health and HIV (BASHH); 2006. 14 p. [40 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Aug (revised 2006 May)

GUIDELINE DEVELOPER(S)

British Association for Sexual Health and HIV - Medical Specialty Society

SOURCE(S) OF FUNDING

Not stated

GUIDELINE COMMITTEE

Clinical Effectiveness Group (CEG)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Author: Philippe Mayaud, Department of Infectious & Tropical Diseases, London School of Hygiene & Tropical Medicine

Clinical Effectiveness Group (CEG) Members: Keith Radcliffe (Chairman); Imtyaz Ahmed-Jushuf; David Daniels; Mark FitzGerald; Neil Lazaro; Guy Rooney

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Conflict of interest: None

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previously released version: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guideline for the management of lymphogranuloma venereum. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. [28 references]

GUIDELINE AVAILABILITY

Electronic copies: Available from the British Association for Sexual Health and HIV Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following background documents are available:

- UK national guidelines on sexually transmitted infections and closely related conditions. Introduction. Sex Transm Infect 1999 Aug;75(Suppl 1):S2-3.
- Revised UK national guidelines on sexually transmitted infections and closely related conditions 2002. Sex Transm Infect 2002;78:81-2.

Print copies: For further information, please contact the journal publisher, BMJ Publishing Group.

The following is also available:

- Improving case ascertainment and awareness raising of lymphogranuloma venereum (LGV) in England amongst men who have sex with men. London (UK): Health Protection Agency. 6 p. Electronic copies: Available from the Health Protection Agency Web site.

Additionally, auditable outcome measures are available in the original guideline document.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on December 8, 2000. The information was verified by the guideline developer on January 12, 2001. This summary was updated on June 24, 2002. This NGC summary was updated by ECRI Institute on December 12, 2007. The updated information was verified by the guideline developer on February 7, 2008.

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